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Original Article

VITAMIN D & OSTEOCALCIN LEVELS IN CHILDREN WITH TYPE 1 DM IN THI_QAR PROVINCE SOUTH OF IRAQ 2019

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ABSTRACT

The vitamin D endocrine system is now recognized as sub serving a wide range of fundamental biological functions in cell differentiation, inhibition of cell growth as well as immunomodulation. Both types of immunity, are regulated by vitamin D. Serum Osteocalcin (OC) is an Osteoblast-derived protein and an established biomarker of bone turnover and formation. Recently, OC has been recognized as an endocrine factor potentially regulating glucose tolerance and energy metabolism . The current study aim to estimating the vitamin D and Oc. levels in children with T1DM in Thi qar province. And to find if there is any significant relation between the control of T1DM and vitamin D and Oc. levels . Cross-sectional case -control study done in Thi qar province in Iraq and data collected from March 2019 to June 2019. The study samples comprised 52 children with type 1 DM (age 1-15 yr.) who visited Diabetic center in Thi qar province, and 52 apparently healthy children selected as a control group from the sibling of patients came with their parents to consultation unit in Bint Al Huda hospital in Nassiryia city with the same age group from (1-15 year) also. Brief clinical history was recorded from all participants. Anthropometric measurements in form of weight, height, BMI was measured. Biochemical analysis of Vit D, Oc. To all participants and HbA1c to all diabetic patients are taken . Statistical analysis was achieved by using SPSS version (25). And the result was HbA1c show significant statistical difference between the different levels of vitamin D. at the p value .019. Children with T1D.M were found to have significant association in term of p value at the 0.057 with Oc. in (-.349-.011)(2-tailed) and this is significant negative correlation . We found most of cases above 5 yrs. and some below 5 yrs. The gender distribution doesn't found statistical association in our study. There was significant statistical association between residence and types of the samples that individuals enrolled where most of the inhabitant from urban areas. We also match cases with doses of insulin per day and we faced 9.6% newly Diagnosed as T1DM from total cases studied, 5.7% with single dose and 21.2% cases with basal bolus regime. So we conclude Vit. D deficiency is common and repletion may improve glycemic control in T1DM. And we recommend by importance of evaluation the level of vit. D and Oc. In T1DM patients and vit. D supplementation may improve glycemic control.

KEYWORDS : Type 1diabetes , Vitamin D3 , Osteocalcin .

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INTRODUCTION

Cross-sectional case – control study done in Thi qar province in Iraq and data collected over 4 months period started from March 2019 to June 2019 .

The study samples comprised Fifty two children with type 1 Diabetes Mellitus (age 1-15 years), who visited Diabetic and endocrinology center in Al-Nassiryia city, Type I diabetes was confirmed according to Diagnostic Criteria for Diabetes Mellitus; Report of the Expert Committee on the Diagnosis and Classification of

Diabetes Mellitus: A position statement of the American Diabetes Association[2], and Fifty two apparently healthy children selected as a control group from the sibling of patients came with their parents to consultation unit in Bint Al Huda hospital in Nassiryia city with the age group from (1-15 year) also.

The cases and control are classified according to agein to three groups that include:- children between 1 year and under 5 years, children between 5-10 years, and children between 11-15 years.

Patients using the following treatments or suffering from one of the following diseases were excluded from the study:-

- Diabetic children treated with Warfarin and Heparin, drugs for osteoporosis such as Calcium, Glucocorticoids, and Anticonvulsants medications.
- Those who have taken supplements or vitamin D during the last 6 months.
- Bone diseases such as multiple myeloma, osteomalacia, Paget's disease, and fracture up to one year.
- Patients with gastrointestinal disorders such as celiac disease, pancreatitis, liver disease[14].
- Patients with abnormal renal function.
- Patients with Anemias and thyroid diseases.
- Children with type 2 D.M.

DATA COLLECTION

Brief clinical history of present and past illness and medical therapy was recorded from all participants.

A special questionnaire was designed for purpose of the study, the following information were recorded:-

- Name, Age, gender and Address
- Duration of illness (Diabetes)
- Modality of treatment :- type and dose of insulin and number of doses .
- Any associated diseases (chronic illness) :- Renal(recurrent UTI), parathyroid diseases, bone disease, liver, GIT. Rickets, and any other diseases mentioned.
- Nutritional status of the patient by calculating body mass index.
- Any calcium supplement or D taken before the test
- Chronic use of any medicine.

Procedures

Weight was measured using electronic digital scales. Height was measured using a wall-mounted stadiometer, and applying weight and height on Growth chart of CDC that specified to gender and determine the growth status of child by percentile.

Body mass index was subsequently calculated by dividing weight over height squared (kg/m^2).

Laboratory Analysis

- Blood samples were assayed for 25-OH vitamin D, carboxylated Osteocalcin and HBA1C calculated to all cases.
- In sterile condition and using possible antiseptic measurements for skin5mls of venous blood was collected from each participant and aliquoted into 2 tubes one of which contains EDTA to obtain plasma. For serum preparation, the blood samples were separated after complete clotting by centrifugation at 4,000 rpm for 5 minutes and serum was separated From EDTA tubes.
- HbA1c was measured using chromatography technique (boronate affinity chromatography). The sera were used to measure the concentrations of Osteocalcin and vitamin D using direct ELISA (Enzyme-Linked Immunosorbent Assay).
- Venous blood was taken and the level of vitamin D (25(OH)D) was measured by ELISA Method.
- We classified the deficiency of vitamin D into the optimal level, mild to moderate deficiency, and severe deficiency as in table 1 in introduction[21].
- We classified also the cases of T1DM into good control, fair control, poor control according to the level of HbA1cas in table 2

Table 2: HbA1C Levels to Determine Control Status(2)

HbA1C	Control status
HBA1C 6-7.5%	Good control
HBA1C 7.6 - 9.9%	Fair control
HBA1C 10% or higher	Poor control

Statistical Analysis

Statistical package for social sciences (SPSS) version (25) was used for data analysis, Descriptive statistic, frequencies, percentages, associations, tests of significance (Chi-square test or Fisher exact test) were used for the analysis of categorical variables. Means and standard deviations were used to present data of continuous variables t, ANOVA test had been used. Correlation and logistic regression analysis were performed to recognize the independent factors.

AP-value < 0.05 was considered statistically significant.

Ethical Consideration

The clinical protocol was approved by the Institutional Review Board for each participating hospital and the Department of Health and Education. This study was conducted in conformity with the guiding principles for research involving humans. Written informed consent and assent were obtained from all parents.

Among 104 cases and control (52 for each group) with mean age (9.538±2.8, 7.058± 2.7) years respectively, there was a significant statistical association between age and types of the samples that individuals enrolled within as shown in tables 1-A. While the gender distribution doesn't show such statistical association as shown in figure 1.

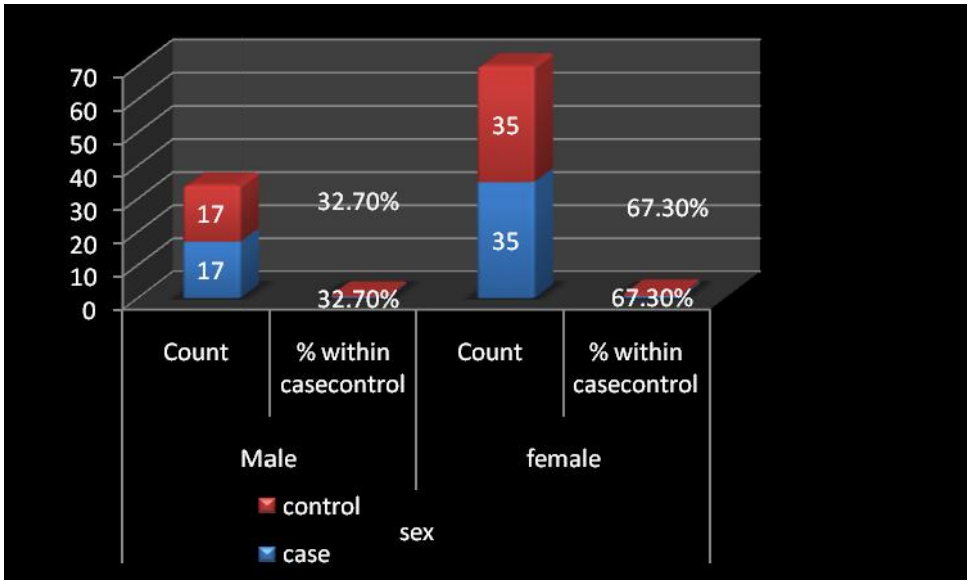

Figure 1: Sex Distribution among the Studied Population.

Table 3-A: Age Difference among Cases and Control

Case control	N	Mean	Std. Deviation	t test, P value
Age of case	52	9.5385	2.80379	4.577
Age of control	52	7.0583	2.72174	0.001

Table 3-B:Distribution of Cases and Control according to Residence of Studied Population

Address		Case control		Total	X2
		Cases (52)	Control (52)	(104)	P value
Urban	No.	35	42	77	7.095
	%address	45.5%	54.5%	100.0%	**0.017**
Rural	No.	8	9	17	
	%address	47.1%	52.9%	100.0%	
Semi-urban	No.	9	1	10	
	%address	90.0%	10.0%	100.0%	
Total	No.	52	52	104	
	%address	50.0%	50.0%	100.0%	

There was significant statistical association between residence and types of the samples that individuals enrolled within as shown in tables 1-B, where most of the in habitants were from urban areas.

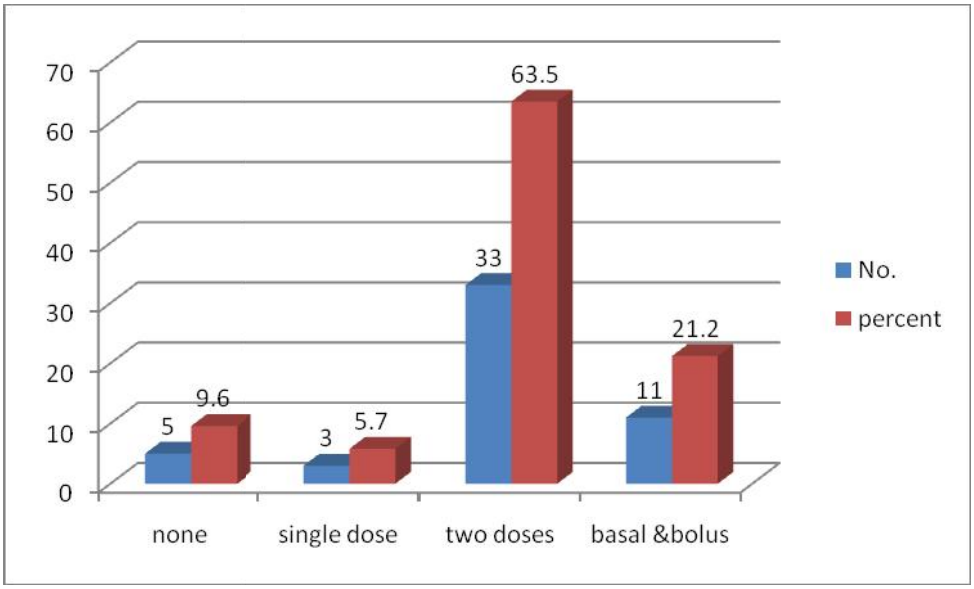

Figure 2: Distribution Accordingto the Number of Inulin Doses.

Most of the cases of T1DM where with two doses of insulin as shown in figure 2.

Table 4: Vitamin D Difference in the Studied Population (Case Control)

Vitamin D			Case control		X^2
			Case	control	P value
	Sever def.	No.	22	21	7.095
		%- Vit. D	42.3%	40.38%	**0.029**
	Mild-Moder.def.	No.	30	25	
		%- vit. D	57.69%	48.07%	
	optimal level	No.	0	6	
		%- Vit. D	0.0%	11.53%	
Total		No.	52	52	104
		%-vit. D	50.0%	50.0%	100.0%

There was significant statistical difference in vitamin D. in different types of the samples, show such association as shown in Table 4.

Table 5: Vitamin D. Difference in the Studied Population (Case and Control)

			D.			Total	X^2
			Sever def.	Mild-Moder.def.	optimal level		P value
Sex							
	Male	No.	13	19	2	34	1.266
		%	38.2%	55.9%	5.9%	100.0%	0.532
	Female	No.	30	36	4	70	
		%	42.9%	51.4%	5.7%	100.0%	
Residence							
Urban		No.	37	35	5	77	
		%	48.1%	45.5%	6.5%	100.0%	

Rural	No.	3	13	1	17	7.307*
	%	17.6%	76.5%	5.9%	100.0%	0.55
Semi-urban	No.	3	7	0	10	
	%	30.0%	70.0%	0.0%	100.0%	

There was no significant statistical difference between vitamin D. and above demographic characters (sex - residence)as shown in table 5.

Table 6: Vitamin D. Difference in the Study Population (Cases only)

		Vit. D			Total	X2 P value
			severe de.	Mild-Moder.		
Sex	Male	No.	6	11	17	0.509
		%	35.3%	64.7%	100.0%	0.186
	Female	No	16	19	35	
		%	45.7%	54.3%	100.0%	
Residence						
Urban	No.	19	16		35	8.822
	%	54.3%	45.7%		100.0%	0.047
Rural	No.	0	8		8	
	%	0.0%	100.0%		100.0%	
Semiurban	No.	3	6		9	
	%	33.3%	66.7%		100.0%	
No treatment	No.	3	2		5	5.963*
	%	60.0%	40.0%		100.0%	0.140
single dose	No.	0	3		3	
	%	0.0%	100.0%		100.0%	
two doses	No.	12	21		33	
	%	36.4%	63.6%		100.0%	
basal &bolus	No.	7	4		11	
	%	63.6%	36.4%		100.0%	
No family history of DM No.	4	9	13			
	30.8%	69.2%	100.0%		100.0%	6.911
Father	0	1	1		1	0.047
	0.0%	100.0%	100.0%		100.0%	
Brother	5	1	6		6	
	83.3%	16.7%	100.0%		100.0%	
Second degree	9	15	24		24	
	37.5%	62.5%	100.0%		100.0%	
More than one	No.	3	4		7	

There was no significant statistical difference invitamin D. indifferent gender, in different types of the samples, while residence, family history of DM show significant statistical association as shown in tables 6.

Table 7: Group Statistics Difference for Association between Some Determinant and Vitamin D Deficiency among Diabetic Patient

Vitamin. D Level		N	Mean	S. D	T	Sig.
Age	Mild-Moder.def.	30	9.3000	2.45511	1.483	.144
	Sever def.	22	9.8636	3.25204	1.295	.210
Disease Duration	Mild-Moder.def.	30	2.4043	2.62757	.028	.977
	Sever def.	22	2.5573	2.07070	.032	.975
HbA1C	Mild-Moder.def.	30	11.0147	2.15242	-2.215-	.031

	Sever def.	22	10.3586	1.59039	-2.462-	.019
BMI	Mild-Moder.def.	22	17.50318	2.906676	-.198-	.845
	Sever def.	30	16.14833	2.638126	-.212-	.833

The HbA1C only show significant statistical difference between the different levels of vitamin D. while there was no such difference with other different determinant Most of our studied population were with poorly control status.

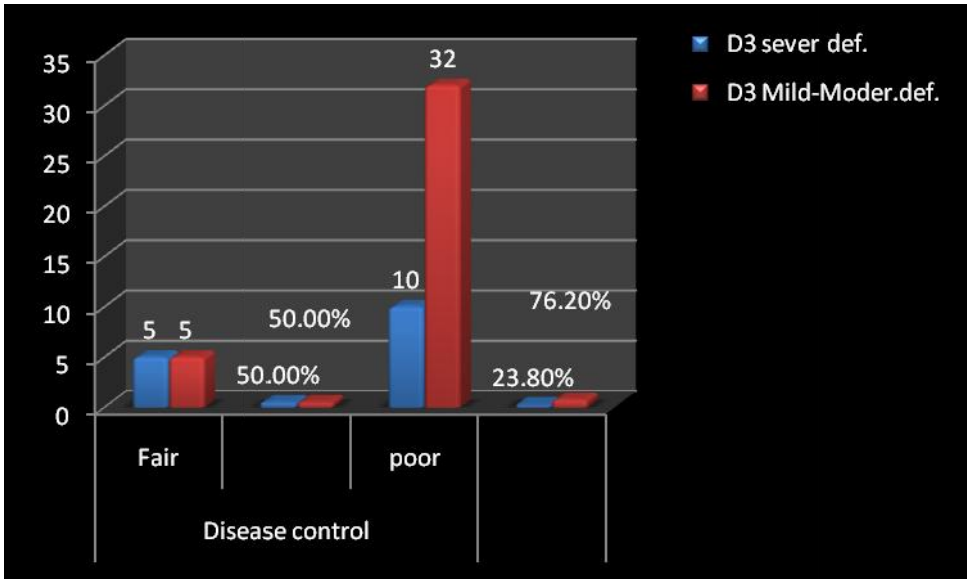

Figure 3: Distribution Accordingto the Disease Control Status.

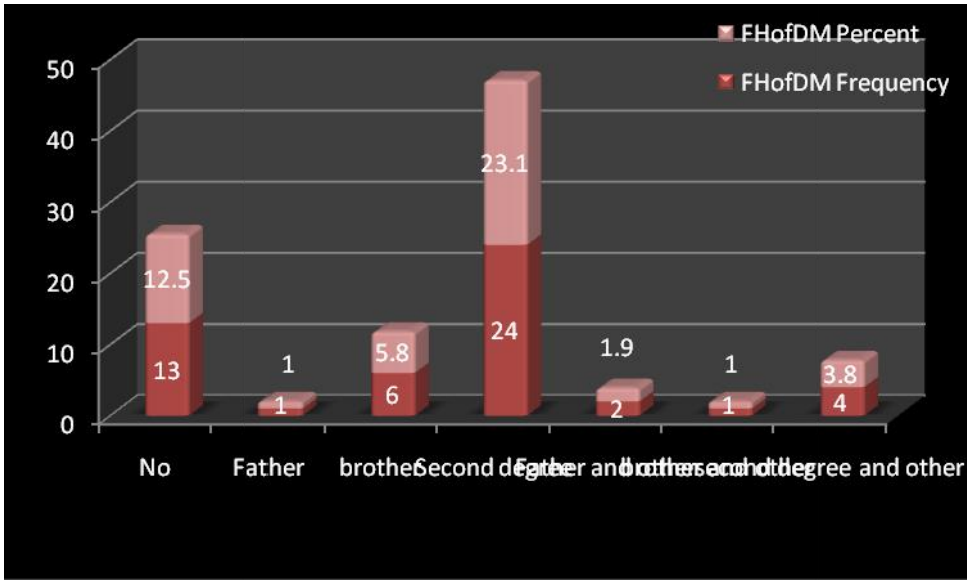

Figure 4: Family History of DM among Diabetic Patients.

Second degree relatives of diabetic patients were the most proportional category of the positive family history in comparison to the others categories the vitamin D. level show significant statistical association with control status.

Table 8: Determinants of the Disease Control (Diabetic Patients) According to HbA1C

Determinants	Disease-Control	N	Mean	S. D	F	Sig.
Age	Fair	10	9.9000	1.85293	3.222	.079
	Poor	42	9.4524	2.99758		
DOD	Fair	10	2.6680	2.14370	.039	.844
	Poor	42	2.4217	2.46295		
BMI	Fair	10	16.6800	2.81561	.028	.867
	Poor	42	16.7314	2.84211		
Vit. D	Fair	10	13.5869	6.05486	5.863	**.019**
	Poor	42	12.1237	3.84695		
Osteocalicin	Fair	10	46.7326	28.6139	.569	.454
	Poor	42	29.4382	22.1297		

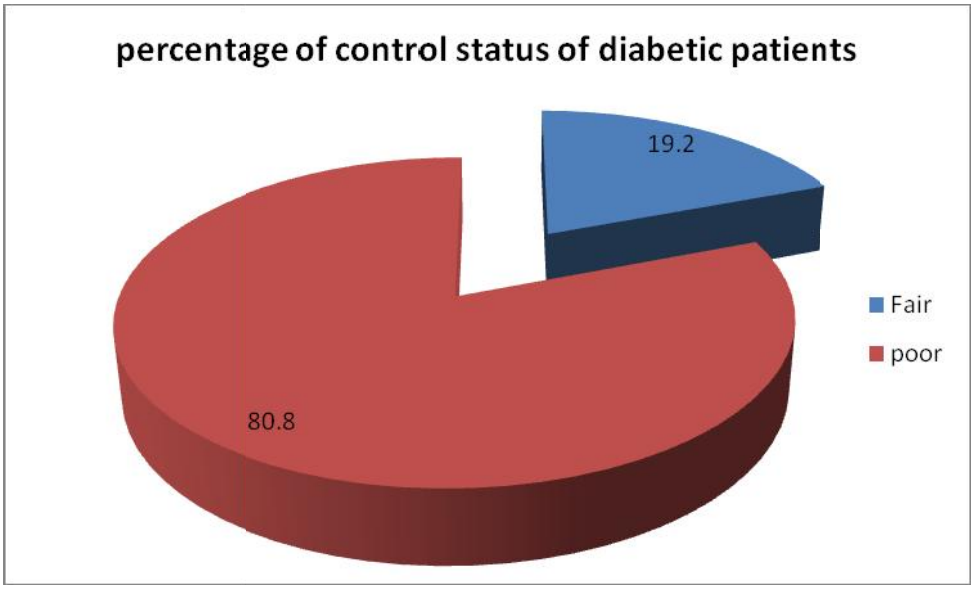

Figure 5: Distribution of Diabetic Patients According to Control Status.

Table 9: Logistic Regression Analysis of Independent Factors

	B	S.E.	Wald	df	Sig.	Exp. (B)
Address	1.176	.509	5.346	1	.021	3.241
Type of treatment	-.590-	.321	3.365	1	.067	.554
BMI	-.152-	.118	1.646	1	.199	.859
HbA1C	.224	.181	1.542	1	.0214	1.251
Sex	-.684-	.785	.759	1	.384	.505
Age	.036	.145	.062	1	.804	1.037
Variable(s) entered on step 1: address, type of treatment, BMI, HbA1C(disease control), sex, age. Logistic regression analysis of qualitative variables were done. There are no significance between these variables according to logistic regression to its						

Table 10: Correlations Regression of Independent Factors for vitamin D. and Osteocalcin

		Vit. D	Osteocalcin	age	DOD	HbA1C	BMI
OSTEO CALICIN	Pearson Correlation	.085	1				
	Sig. (2-tailed)	.548	52				
Age	Pearson Correlation	-.136-	.040	1			
	Sig. (2-tailed)	.337	.779	52			
Duration	Pearson Correlation	-.125-	.001	.262	1		
	Sig. (2-tailed)	.379	.992	.061	52		
HbA1C	Pearson Correlation	-.152-	-.349-*	.067	.131	1	
	Sig. (2-tailed)	.028	.011	.635	.355	52	
BMI	Pearson Correlation	-.224-	-.123-	.434**	.416**	.095	1
	Sig. (2-tailed)	.111	.385	.001	.002	.502	52

Correlation regression for quantitative variables :-
*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed)

Table 11

Group Statistic					
	VAR00001	N	Mean	Std. deviation	Std. Error Mean
Osteocalcin	Case : 1.00	52	32.7640	24.19825	3.35569
	Control :2.00	52	38.7321	18.39346	2.55071

In table 11: statistical classification of cases and control groups according to level of Osteocalcin.

Table 12: Osteocalcin between Diabetic and Control Group

Independent Samples Test										
		Levene's Test for Equality of variances		T- test for Equality of Means						
		F	Sig.	T	df	Sig. 2 tailed	Mean difference	Std. Error Difference	95% Confidence interval of the difference	
									lower	upper
Osteo calcin	Equal variances assumed	3.717	**0.057**	-1.416-	102	.160	-5.96810-	4.21507	-14.32867-	2.39248
	Equal variances not assumed			-1.416-	95.184	.160	-5.96810-	4.21507	-14.33586 -	2.39967

Table 12:- show significant correlation at the p value 0.057 between diabetic and Osteocalc in.

DISCUSSIONS

Among 52 cases and 52 control with mean age (9.538±2.8, 7.058± 2.7) years respectively, there was significant statistical association between age and types of the samples that individuals enrolled within faced most of the cases above 5 yr. and

some of the cases below 5 yr. and that expected because Peaks of presentation occur in 2 age groups: at 5-7 yr. of age and at the time of puberty[2].

And this is similar to what found in The cohort study by Şükran Poyrazoğlu1, Rüveyde Bundak (eds)[54]. This study showed increased T1DM with age in both sexes and was highest in the 5-14 year age group and followed by a decrease in the 15–17 year age group. The youngest age group (0-4 years) had lower incidence as compared with older children (5-14 years). Age difference has been shown in other counties[55]. DiaMond study showed that 5-9 year old children had a higher risk of developing T1DM compared with 0-4 year old children[56]. Some counties reported high incidence in 5-9 years old, but others found the highest incidence in children aged 10-14 years[54].

Age differences in T1DM incidence have also been observed in previous studies[57]

Matching on factors such as age and sex is commonly used in case-control study and also used in our study intended to eliminate confounding, the main potential benefit of matching in case-control studies is a gain in efficiency. Methods for analyzing matched case-control studies have focused on utilizing conditional logistic regression models that provide conditional and not causal estimates of the odds ratio

The gender distribution doesn't found such statistical association in our study.

And when compare our result with previous cohort study[54], although the mean annual incidence of boys and girls was similar, a male predominance was seen in all age groups except for 5-9 years, The female predominance in 5-9 year age group could be due to the earlier onset of puberty in girls than in boys[54].

However, no significant difference in T1DM incidence between boys and girls was observed in Shanghai and Kuwait[58,59].

There was significant statistical association between residence and types of the samples that individuals enrolled where most of thein habitants from urban areas and can be explained by The Hygiene Hypothesis: Possible Protective Role of Infections, The hygiene hypothesis states that T1DM is a disease of industrialized countries[2].

We also match cases in our study with doses of insulin taken per day and the Distribution according to the number of inulin doses as shown in figure 2 and we faced 9.6% newly Diagnosed as T1DM from total cases studied and 5.7% with single dose and that because the family was poor compliance with the counseling in diabetic center; 21.2% cases with basal bolus regime of insulin and that because frequent injection was not prefer by most diabetic patients so most of cases studied with two doses of insulin mixtard at morning and evening.

There was significant statistical difference at the p value <0.05 invitamin D in different types of the samples, show such association in tables 2, P value 0.029.

And the close numbers of cases and control group that show deficiency in vit. D because; vitamin D deficiency is so common in all age group because decreasing sun exposure in recent decades due to many causes; and the small sample size didn't giveus sufficient idea about vit. D deficiency and incidence of T1DM.

In table 4 : We matched the degree of disease control according to HbA1C as mentioned in chapter 2 as table 2[2]; and Categorization of Vitamin D Levels as mentioned in introduction table 1[21]. And we found significant statistical association (p value .019) between the different levels of vitamin D and degree of disease control (according to HbA1C) while there was no such difference with other different determinants in table 8.

The association between vit D. and degree of disease control according to HBA1C as shown in table 4, we found The HbA1C only show significant statistical difference between the different levels of vitamin D while there was no such difference with other different determinants like Age, duration of disease and BMI, and thes ignificance 0.019.

There is growing evidence that vitamin D deficiency could be a contributing factor in the development of both type 1 and type 2 diabetes[(25)].

Evidence in many studies indicated that :-

- Vitamin D treatment improves glucose tolerance and insulin resistance[(60,61)]
- Vitamin D deficiency leads to reduced insulin secretion[(62)].
- Vitamin D contributes to normalization of extracellular calcium, ensuring normal calcium flux through cell membranes; therefore, low vitamin D may diminish calcium's ability to affect insulin secretion[(63).]
- Other potential mechanisms associated with vitamin D and diabetes include improving insulin action by stimulating expression of the insulin receptor, enhancing insulin responsiveness for glucose transport, and improving systemic inflammation by a direct effect on cytokines[(14)].

Similarity to what discuss in study of Ghada A Mohamed, department of internal medicine Assiut University Po, Egypt 2016 there were high mean HbA1cand there was significant inverse correlation between HbA1c and vitamin D among the participants (r=−0.374 and P=0.003)[(64)].

Children with type 1 D.M were found to have significant association in terms of p value at the 0.05 between HBA1c and Osteocalc in in diabetic patients as in Table 10 (-.349-.011)(2-tailed) and this significant negative correlation was seen in the research of Mohammed Ayed Huneif1, Department of Pediatrics, College of Medical Applied Sciences, Najran University, Najran, Saudi Arabia at 2017 regarding the correlation between OC and HbA1c in children with type 1 diabetes mellitus (T1DM), our study displayed a significant negative correlation (r=-0.182, p <0.037) between these parameters indicating the lower OC, the worse glycaemic control in children with T1DM. Moreover, Khoshhal et al. detected significantly lower levels of procollagen Nterminal peptide and osteocalcin in children with T1DM[(65)]. They noticed that serum levels of osteocalcin in type 1 diabetic children deficient when compared with that in healthy control children[(65)].

And similarity to our study when we found There was significant statistical association between D.M and Osteocalcin at p value **0.057** as shown in table 12.

While In the study of: Napoli N, Strollo R, Pitocco D, Bizzarri C, Maddaloni E, et al. (2013) Effect of Calcitriol on Bone Turnover and Osteocalcin in Recent-Onset Type 1 Diabetes find that OC levels were unrelated to b-cell function and other metabolic parameters suggesting that OC is ineffective to control pancreatic function in presence of aggressive autoimmune destruction[(66)].

Osteocalcin significantly diminished in children with T1DM in our study and that describe the influence of Osteocalcin on β cells.

There was no significant statistical difference in vitamin D in the demographic characters, family history of DM in different types of samples.

There was no significant statistical difference invitamin D. indifferent gender, in different types of samples.

Most of our studied population with poorly control status and this may be because of poor compliance or because of poor dietary control.

Limitations

Some of the most important to mention limitations are :-

- The small sample size in endocrinology center meets the inclusion criteria of the research and accepted to include in our research.
- The availability and cost effectiveness of the investigations required in my research.
- The poverty of researches and articles about the relation of DiabeteswithOsteocalcin and vit. D.
- The wide range of vit. D deficiency in all population not only in Diabetic patients.

CONCLUSIONS

- From the current study, we conclude that there is a significant statistical relation between The HBA1C and the different levels of vitamin D.
- Children with type 1 D.M were found to have significant association in term of p value at the 0.057 between HbA1c and Osteocalcin in diabetic patients (-.349-.011)(2-tailed) and this significant negative correlation.

The link between Osteocalcin and energy metabolism suggested in general, metabolic diseases are known to influence bone homeostasis.

RECOMMENDATIONS

- Low level of Vit. D in type 1D.M is extremely highly and closely correlated to HbA1C, we recommended that evaluation of the level of vit. D in type 1 Diabetic patients is very important.
- Vitamin D deficiency is commons, inexpensive and readily available and repletion might improve glycemic control in type 1 Diabetes.
- Well-designed clinical studies are required to ascertain if improving 25-OHD levels from deficiency to sufficiency improves glycemic control in patients with type 1 diabetes

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